DOCKET NO.: WYNC-0677 (AM100299CON) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Adam M. Gilbert and Gary P. Stack

Confirmation No.: **3576**

Serial No.: **10/663,533**

Group Art Unit: **1625**

Filing Date: **09/16/2003**

Examiner: **Taylor V. Oh**

For: **8-AZA-BICYCLO[3.2.1]OCTAN-3-OL DERIVATIVES OF 2,3-DIHYDRO-1,4-BENZODIOXAN AS 5-HT_{1A} ANTAGONISTS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

Appellant submits this Reply in response to the Examiner's Revised Answer dated August 3, 2007 in connection with the above-identified application. This reply is being filed within two months of said answer.

The Examiner's Revised Answer does not provide sufficient basis either for doubting the correlation between Appellant's *in vitro* assay data and *in vivo* $5HT_{1A}$ serotonin receptor antagonist activity, or for questioning the nexus between $5HT_{1A}$ antagonism and the treatment of Alzheimer's disease, disorders of thermoregulation, and sleep dysfunction.[1] Accordingly, the Examiner has not met its burden to provide reasons for the alleged lack of enablement of the currently pending claims, and the instant rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

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[1] To expedite resolution of the instant matter, Appellant previously submitted an amendment under 37 C.F.R. § 1.116 that deleted from claim 26 the method of using the described compounds to provide treatment for conditions relating to appetite control. (*see* 9/12/05 Amendment After Final Rejection). Accordingly, the present paper does not address the Office's contentions with respect to the enablement of methods of treatment of conditions relating to appetite control.

The Examiner has supplied no new evidence that serves to contradict the art-recognized correlation between the *in vitro* assays that are utilized by the present application to demonstrate the efficacy of the instant compounds for $5HT_{1A}$ receptor antagonism (*see* Appellant's Brief at page 8) and *in vivo* activity, and as such, the Examiner has still not met its burden of providing specific reasons for its conclusion of a lack of correlation between the *in vitro* and *in vivo* models. *See* M.P.E.P. 2164.02 (also providing that the application must provide only a reasonable, as opposed to a "rigorous or an invariable exact", correlation between *in vitro* and *in vivo* models). The Examiner asserts that because the studies described in Lanfumey *et al.* and Kwon *et al.* involve $5HT_{1A}$ antagonists that are "structurally different" than the instant compounds, the *in vivo* activity demonstrated by such studies is not properly suggestive of *in vivo* activity by the instant compounds (*see* Examiner's Revised Answer at page 6). However, this line of argument reflects a failure to recognize that the relevant characteristic shared between the compounds described in the Lanfumey *et al.* and Kwon *et al.* studies and the present compounds is *$5HT_{1A}$ antagonist activity*, and that structure in of itself is not a proper means of distinguishing the present compounds from those recognized by skilled artisans as possessing potent *in vivo* activity. Thus, there is no evidence of record that is sufficient to prompt any doubt that the current claims lack enablement in this respect.

It is also the case that those skilled in the art recognize the nexus between $5HT_{1A}$ antagonism and the treatment of the conditions recited in the claims presently on appeal. To advance a contrary position, the Examiner appears to rely heavily on one reference, Barnes *et al.*, which provides a review of several studies that examined the effect of $5HT_{1A}$ agonists on hypothermia in rodents. While not mentioned by name, the Barnes *et al.* reference was generally addressed when Appellant noted that the role of the $5HT_{1A}$ serotonin receptor in thermostasis and thermoregulation is recognized among those skilled in the art, *e.g.*, serotonin excess as induced by $5HT_{1A}$ agonists directly disrupts thermoregulation, and alleviating the condition of serotonin excess can be expected to result in the mitigation of the condition of thermoregulatory disruption (*see* 9/12/2005 Appellant's Answer at page 4). Appellant additionally notes that the portion of Barnes *et al.* that is cited by the Examiner is directed to addressing the apparent uncertainty with respect to whether the mechanism underlying the

hypothermic effect of $5HT_{1A}$ receptor antagonists is presynaptic or postsynaptic, and that Barnes *et al.* prefaces its discussion of this issue with an acknowledgement that the nexus between the $5HT_{1A}$ receptor and certain behavioral responses, including thermoregulation, "is clear" (*see* Barnes *et al.* at page 1092, first column; "Whilst the involvement of the 5-HT_{1A} receptors in many of these responses is clear, particularly on the basis of more recent studies with selective 5-HT_{1A} receptor antagonists . . ., in some cases controversy exists regarding the involvement of pre- (5-HT_{1A} autoreceptors) or postsynaptic mechanisms.")[2]. Thus, Appellant's 9/12/2005 Answer generally addressed Barnes *et al.*, and the current paper reiterates specific reasons why the Examiner's reliance on Barnes *et al.* to demonstrate an alleged divergence between the claimed conditions and $5HT_{1A}$ receptor antagonism is inapposite.

The Examiner has also failed to cast reasonable doubt on the evidentiary record created by the Appellant. Prior to appeal, Appellant submitted several references that demonstrate the appreciation among those skilled in the art that a clear nexus exists between $5HT_{1A}$ receptor antagonism and Alzheimer's disease, disorders of thermoregulation, and sleep dysfunction (*see* Appellant's 12/20/04 Reply to the Office's 9/21/04 Final Rejection). The Examiner has also entered and considered the seven references that were submitted with Appellant's Appeal Brief.

The Examiner has stated that it has not considered the Lanfumey *et al.* and Kwon *et al.* references to the extent that they have been cited for the purpose of providing additional evidence of the existence of a nexus between $5HT_{1A}$ receptor antagonism and Alzheimer's disease (*see* 8/3/07 Revised Examiner's Answer at page 10). However, even if these references are not taken into account, it is still the case that the Examiner has failed to present any objective evidence to the effect that the relevant nexus does not exist, and as such the Examiner's position does not meet a basic requirement for presenting a *prima facie* case of lack of enablement. *See* M.P.E.P. § 2164.04 (stressing that "specific technical reasons are always required [to present a *prima facie* case]"). In fact, the Examiner has repeatedly glossed over the putative technical basis for the contention that the prior art fails to show a

[2] *See also* pages 8-9 of Appellant's 12/20/04 Reply to the Office's 9/21/04 Final Rejection.

relationship between $5HT_{1A}$ receptor antagonism and Alzheimer's disease – for example, in the Revised Examiner's Answer, the Examiner's position as to the "state of the prior art" is substantively provided with respect to appetite control, disorders of thermoregulation, and sleep dysfunction, but there is no specific discussion with respect to Alzheimer's disease (*see* 8/3/07 Revised Examiner's Answer at page 7). Similarly, the Examiner provides argument as to why Schechter *et al.* allegedly does not show a nexus between $5HT_{1A}$ receptor antagonism and Alzheimer's disease, but does not proffer any technical evidence or reasoning to support its position as to the alleged nonexistence of this nexus (*see id.* at page 11; *see also* 7/11/2005 Examiner's Answer at page 9). Frankly, Appellant would be surprised if the Examiner would have come forward with such evidence, as the prior art is replete with scientific findings as to the nexus between $5HT_{1A}$ receptor antagonism and Alzheimer's disease.[3, 4] Accordingly, the Examiner has failed to meet its burden to present evidence to contradict the clear nexus between $5HT_{1A}$ receptor antagonism and Alzheimer's disease, and the rejection of the claims on the ground that this nexus does not exist cannot stand.

The Examiner acknowledges that there exists a nexus between $5HT_{1A}$ receptor antagonism and hypothermia (*see* 8/3/07 Revised Examiner's Answer at page 10, saying of the Ootsuka et al. reference that "this reference may support a claim drawn to hypothermia"), and that the Brubacher *et al.* reference establishes that excess serotonin associated with

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[3] *See, e.g.,* Harder JA *et al.*, Psychopharmacology (Berl). 1996 Oct;127(3):245-54, at Abstract ("Since cholinergic loss in the hippocampus (and neocortex) occurs in association with cognitive decline in **Alzheimer's disease**, these results suggest that **5-HT1A antagonists** may have a role in the treatment of some of the cognitive symptoms of dementia."); Francis PT, Neurodegeneration. 1996 Dec;5(4):461-5, at Abstract ("Specifically, it is proposed that cholinomimetics used for the symptomatic treatment of **AD [Alzheimer's Disease]** may work by influencing the activity of pyramidal neurones and that this action may be potentiated by a **5-HT1A antagonist**."); Harder JA *et al.*, Neuropharmacology. 2000 Feb 14;39(4):547-52, at Abstract ("In **Alzheimer's disease**, cognitive decline is associated with loss of both glutamatergic and cholinergic neurons . . . the cognitive effects of glutamatergic blockade can be overcome by treatment with a **5-HT1A antagonist**.").

Although the Appellant did not specifically submit these references in connection with its previous responses, Appellant has maintained throughout the prosecution that those skilled in the art, including the present inventors, were aware of the nexus between $5HT_{1A}$ receptor antagonism and Alzheimer's disease at the time of the effective filing date of the instant application. The above references therefore serve a corroborative purpose.

[4] Appellant also reminds the Board that the present claims are not directed to the absolute "cure" of Alzheimer's disease or the other listed conditions, but rather the *treatment* thereof, which encompasses the alleviation of any of the symptoms or phenotypic characteristics of a condition. To the extent that the Examiner asserts that "[i]t is the state of the art that there is no known cure or prevention for a neurodegenerative disease such as Alzheimer's disease" (*see* 4/14/04 Office Action at page 3) or for any of the other conditions listed in the pending claims, such assertion reflects the use of an undue enablement standard and is not relevant to the status of the present claims under 35 U.S.C. § 112, first paragraph.

hyperthermia results from excessive stimulation of $5HT_{1A}$ (*see* 8/3/07 Revised Examiner's Answer at page 11, acknowledging that "Brubacher *et al.* teach that excessive stimulation of $5HT_{1A}$ leads to excess serotonin associated with hyperthermia"), *i.e.*, that a functional relationship exists between hyperthermia and a condition that the present compounds are empirically known to alleviate. The Examiner therefore effectively acknowledges that $5HT_{1A}$ antagonism bears a nexus with two seemingly opposite thermoregulatory disorders.

The Examiner also acknowledges that there exists a nexus between $5HT_{1A}$ receptor antagonism and induction of REM sleep (*see* 8/3/07 Revised Examiner's Answer at page 10, saying of the Sorensen et al. reference that "this reference may support a claim drawn to narcolepsy"), but incorrectly concludes that neither Bjorvatn *et al.* nor Gillin *et al.* show that $5HT_{1A}$ receptor agonists are capable of inducing sleep; in fact, Bjorvatn *et al.* specifically provides that "Intrathecal administration of selective 5-HT1A agonist produces an increase in SWS [slow wave sleep]" and that "Microdialysis perfusion of a selective 5-HT1A agonist into the dorsal Raphe nucleus causes in increase in REM sleep" (*see* Bjorvatn *et al.* at Abstract). Accordingly, the Examiner's conclusions regarding whether one skilled in the art would use a $5HT_{1A}$ antagonist to either increase sleep or decrease sleep (*i.e.*, provide the opposite effect of $5HT_{1A}$ agonists, as clearly documented in the relevant literature) are incorrect.

More generally, the preceding discussion and the evidence presented by Appellant demonstrate that the Examiner is wrong to conclude that compounds that effect a change in $5HT_{1A}$ receptor activity "generally do not evoke opposing results", since those skilled in the art in fact recognize that the contrary is true. Likewise, the Examiner's Revised Answer does not proffer additional bases for casting reasonable doubt on the evidentiary record created by the Appellant or otherwise reaching a conclusion that would justify a rejection of the claims for lack of enablement.

Because the rejected claims are sufficiently enabled, Appellant respectfully requests that the rejection of claims 26 and 33-52 under 35 U.S.C. § 112, first paragraph be reversed.

Date: October 3, 2007

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